

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of : *West et al.*
Application No. : 10/576,956
Filing Date : November 27, 2006
Art Unit : 1625
Title : Cyanine Dye Labelling Reagents
Docket No. : PL0379 US

Mail Stop Appeal Brief–Patents
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

APPEAL BRIEF

Table of Contents

	<u>Page</u>
I. Real Party In Interest	3
II. Related Appeals and Interferences.....	3
III. Status of Claims	3
IV. Status of Amendments	3
V. Summary of Claimed Subject Matter	3
VI. Grounds Of Rejection To Be Reviewed On Appeal	5
VII. Argument	6
The Examiner's Rejection of Claims 1-6 and 10-14 Should be Reversed Since, Leung Fails to Disclose, Teach or Suggest All the Elements of Claims 1-6 and 10- 14.....	6
VIII. Claims Appendix	11
IX. Evidence Appendix.....	19
X.....Related Proceedings Appendix.....	20

I. REAL PARTY IN INTEREST

The party in interest in this Appeal is GE Healthcare, Inc., a part of General Electric ("GE").

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences related to the instant appeal.

III. STATUS OF CLAIMS

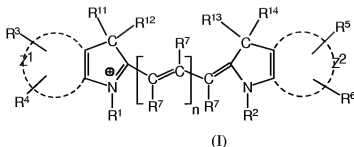
Claims 1-6 and 10-14 are pending in this application. The Examiner has rejected all of these claims. Claims 1-6 and 10-14 as amended during prosecution are reproduced in the **Claims Appendix** attached hereto. Appellants are appealing the rejection of Claims 1-6 and 10-14.

IV. STATUS OF AMENDMENTS

Appellants submitted an Amendment After Final on June 16, 2009. No claims have been amended thereafter. An Advisory Action Before the Filing of an Appeal Brief was mailed on July 22, 2009 by the Examiner.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent Claim 1 describes a compound of formula (I):



wherein:

Z^1 and Z^2 independently represent the carbon atoms necessary to complete a one ring, or two-fused ring aromatic system;

R^1 and R^2 are independently chosen from the group $-E-F$, $C_1 - C_6$ alkyl, benzyl either unsubstituted or substituted with sulphonic acid, and the group $-(CH_2)_k-W$,

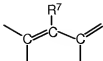
where W is sulphonic acid or phosphonic acid and k is an integer from 1 to 10;

R^3 and R^4 are attached to the Z^1 ring structure and groups R^5 and R^6 are attached to the Z^2 ring structure, and $n = 1, 2$ or 3 ;

R^3 , R^4 , R^5 and R^6 are independently selected from the group $-E-F$, hydrogen and sulphonic acid;

each R^7 is independently the group $-E-F$, hydrogen or two of R^7

together with the group,



form a hydrocarbon ring system having 5 or 6 atoms;

each R^{11} , R^{12} , R^{13} and R^{14} is independently a group $-(CH_2)_k-W$ as defined above, or $C_1 - C_6$ alkyl;

E is a single bond or a spacer group having a chain from 1–20 linked atoms selected from the group consisting of carbon, nitrogen and oxygen atoms and F is a target bonding group;

wherein F is either:

- (i) a reactive group selected from carboxyl, succinimidyl ester, sulpho-succinimidyl ester, isothiocyanate, maleimide, haloacetamide, acid halide, hydrazide, vinylsulphone, dichlorotriazine and phosphoramidite; or
- (ii) a functional group selected from hydroxy, amino, sulphhydryl, carbonyl (including aldehyde and ketone) and thiophosphate; or
- (iii) an affinity tag;

with the provisos that:

- (a) one of groups R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 is the group $-E-F$;
- (b) one or more of R^{11} , R^{12} , R^{13} and R^{14} is the group $-(CH_2)_k-W$;
- (c) the compound of Formula I has from 3 to 5 sulfonic acid groups.

Support for this claim can be found on pages 3-5 of the published specification, (WO2005/044923).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues for review in this appeal arise from an Advisory Action Before Filing of an Appeal Brief dated July 22, 2009. The Examiner rejected claims 1-6 and 10-14 under 35 U.S.C. § 103(a) as allegedly being unpatentable over *Leung et al.*, US Patent No. 6,974,873 (“Leung”).

Therefore, the issue in this appeal is:

1. Whether Leung discloses, teaches, or suggests all the elements of claims 1-6 and 10-14?

VII. ARGUMENT

The Examiner rejected Claims 1-6 and 10-14 under 35 U.S.C. § 103 (a) as allegedly being unpatentable over *Leung et al.*, US Patent No. 6,974,873 (“Leung”).

Appellants respectfully request that the Board should reverse the Examiner’s rejection for the reasons set forth below.

A. The Examiner’s Rejection of Claims 1-6 and 10-14 Should be Reversed Since Leung Fails to Disclose, Teach or Suggest All the Elements of Claims 1-6 and 10-14.

The Examiner’s Rejections of Claims 1-6 and 10-14 should be reversed since Leung fails to disclose, teach, or suggest all the elements of claims 1-6 and 10-14.

In the Advisory Action dated July 22, 2009, the Examiner states that “Leung’s disclosure is not limited to preferred embodiments”. Appellants argue that the embodiments disclosed, taught, or suggested in Leung are not disclosed, taught, or suggested in the current invention. Appellants respectfully point out here that it is well settled in the law that a reference must be

considered not just for what it expressly teaches, but also for what it fairly suggests to one who is unaware of the claimed invention. *In re Baird*, 16 F.3d 380, (Fed. Cir. 1994). For example, claim 1 of the present invention stipulates at proviso (c), that the compound/dye must have 3 to 5 sulfonic acid substituents. Leung does not disclose, teach or suggest that feature. Leung teaches that sulfonation of the dyes is an optional feature. Only at Column 10 lines 53 to 54 does Leung suggest that, in one aspect, the dyes “are sulfonated one or more times”. Leung mentions (Column 10 line 64 following) in the context of attaching the reactive group at R³ only, sulfonation at least 4 times. That is specifically at R⁷, R¹⁷ and sulfoalkyl at R² and R¹³. That combination is outside the scope of the present claims.

A further essential feature of present claim 1 is that only one group –E-F is attached. In contrast, Leung makes that feature optional. Hence, there could be zero such groups in Leung. There could also be a large number of them - since such a group is an optional definition for almost all the R groups of Leung. Leung does teach (Column 12 lines 1 to 11) that, “in one embodiment” at least one such group should be present. That is, however, merely one of many preferred embodiments of Leung and the general teaching of Leung therein is much broader as described above.

A further feature of present claim 1 is that at least one of R¹¹ to R¹⁴ of Formula I is required to be -(CH₂)_k-W and the remainder are required to be C₁₋₆ alkyl. See proviso (b) of claim 1. Leung does not disclose, teach or suggest that combination of features. Instead, the R³/R⁴/R¹³/R¹⁴ groups of Leung are freely chosen from a long list of possibilities.

Present Formula I also specifies the combination that, when R^1/R^2 is not $-E-F$, it is chosen from C_{1-6} alkyl, $-(CH_2)_k-W$ or benzyl (optionally substituted with sulfonic acid). Leung does not disclose, teach or suggest that combination. The corresponding groups of Leung (R^2 and R^{12}) are independently chosen from a long list of possibilities (Leung Columns 4 lines 24 to 54). Leung in fact teaches that it is preferred that R^2 and R^{12} are the same (Column 4 lines 54-55).

The present invention also teaches that the group $-E-F$ can be located at the R^7 groups of Formula I. Leung does not disclose, teach or suggest that feature. Leung describes the BRIDGE at Column 6 line 47 ff (Formula VIII therein). The definitions of R^{21-27} (*ibid*, Column 6 line 66 to Column 7 line 16), in Leung exclude that possibility.

The compounds of Formula I of present claim 1 are thus believed to have several features and/or combinations of features not disclosed, taught or suggested by Leung. These features make the invention much more than mere “positional isomers of Leung’s compound” as suggested by the Examiner in a previous Office Action dated April 16, 2009.

In the Office Action dated April 16, 2009, the Examiner also alleges that “the structural backbone of the cyanine molecule” are the same. Appellants point out that the basic skeleton of cyanine dyes has indeed been known for some decades. That has not, however, prevented patenting in the area and many hundreds of patents have been granted on cyanine dye type molecules. See e.g. Leung at Column 1 lines 16 to 48, plus Column 2 lines 19 to 28 for an illustration of patent activity in the field. A person skilled in the art would know that dye

chemistry is such that small changes in both substituent pattern and choice of substituents can have profound effects on the properties of a given dye for a particular application. Leung itself provides an illustration of the subtle effects of substituents – see Column 1 line 49 to Column 2 line 16 of Leung. The dyes of present claim 1 have useful improved properties – see page 11 lines 4 to 14 of the specification.

Additionally, the compounds encompassed by the formula of Leung at Column 3 lines 24 to 34 are vast in scope and thus do not teach toward the present invention. With reference to A (Formula I) and B (Formula VII) therein, X and Z are defined to be:



where X and Z are the same or different (Leung Column 4 lines 16 to 23 plus Column 6 lines 4 to 16). Since X and Z can be the same or different, there are 25 combinations of classes of dye.

Only one of those corresponds to present claim 1 ($X = -CR^3R^4-$ and

$Z = -CR^{13}R^{14}-$). Accordingly, Appellants wish to point out that “The prior art itself must provide a motivation or reason for the worker in the art, without the benefit of the Applicant’s specification, to make necessary changes in the reference device”. See, *Ex parte Chicago Rawhide Manufacturing Co.*, 226 U.S.P.Q. 438 (PTO Bd. App. 1984).

In view of the foregoing, it is respectfully submitted that the 35 U.S.C. § 103 rejections of claims 1-6 and 10-14 over Leung be withdrawn.

CONCLUSION

Appellants respectfully request that the Board reverse the rejection of Claims 1-6 and 10-14 as set forth in the final Advisory Action Before the Filing of an Appeal Brief mailed July 22, 2009, that the Board allow the pending claims since they are in condition for allowance, and that the Board grant any other relief as it deems proper.

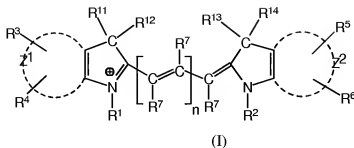
Dated: October 20, 2009

Respectfully submitted,

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VIII. CLAIMS APPENDIX

Claim 1. A compound of formula (I):



wherein:

Z^1 and Z^2 independently represent the carbon atoms necessary to complete a one ring, or two-fused ring aromatic system;

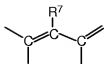
R^1 and R^2 are independently chosen from the group $-E-F$, $C_1 - C_6$ alkyl, benzyl either unsubstituted or substituted with sulphonic acid, and the group $-(CH_2)_k-W$,

where W is sulphonic acid or phosphonic acid and k is an integer from 1 to 10;

R^3 and R^4 are attached to the Z^1 ring structure and groups R^5 and R^6 are attached to the Z^2 ring structure, and $n = 1, 2$ or 3 ;

R^3 , R^4 , R^5 and R^6 are independently selected from the group $-E-F$, hydrogen and sulphonic acid;

each R^7 is independently the group $-E-F$, hydrogen or two of R^7 together with the group,



form a hydrocarbon ring system having 5 or 6 atoms;

each R^{11} , R^{12} , R^{13} and R^{14} is independently a group $-(CH_2)_k-W$ as defined above, or $C_1 - C_6$

alkyl;

E is a single bond or a spacer group having a chain from 1–20 linked atoms selected from the group consisting of carbon, nitrogen and oxygen atoms and F is a target bonding group;

wherein F is either:

- (i) a reactive group selected from carboxyl, succinimidyl ester, sulpho-succinimidyl ester, isothiocyanate, maleimide, haloacetamide, acid halide, hydrazide, vinylsulphone, dichlorotriazine and phosphoramidite; or
- (ii) a functional group selected from hydroxy, amino, sulphhydryl, carbonyl (including aldehyde and ketone) and thiophosphate; or
- (iii) an affinity tag;

with the provisos that:

- (a) one of groups R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 is the group $-E-F$;
- (b) one or more of R^{11} , R^{12} , R^{13} and R^{14} is the group $-(CH_2)_k-W$;
- (c) the compound of Formula I has from 3 to 5 sulfonic acid groups.

Claim 2. A compound according to claim 1 wherein at least two of R^{11} , R^{12} , R^{13} and R^{14} are independently $-(CH_2)_k-W$.

Claim 3. A compound according to claim 1 wherein one of groups R^{11} and R^{12} and one of groups R^{13} and R^{14} is the group $-(CH_2)_k-W$.

Claim 4. A compound according to claim 1 wherein W is sulphonic acid.

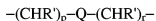
Claim 5. A compound according to claim 1 wherein $-(CH_2)_k-W$ is selected from $-(CH_2)_3-SO_3H$ and $-(CH_2)_4-SO_3H$.

Claim 6. A compound according to claim 1 wherein Z^1 and Z^2 are selected from phenyl and naphthyl moieties.

Claims 7-9. (cancelled)

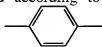
Claim 10. A compound according to claim 1 wherein said target bonding group F comprises an affinity tag.

Claim 11. A compound according to claim 1 wherein said spacer group E is selected from:



where Q is selected from: $-CHR'-$, $-NR'-$, $-O-$, $-CR'=CR'-$, $-C(O)-NR'-$ and $-C(O)-O-$; R' is hydrogen or $C_1 - C_4$ alkyl, p is 0 – 5 and r is 1 – 5.

Claim 12. A compound according to claim 11 wherein Q is selected from: $-CHR'-$, $-C(O)-NH-$ and



; where R' is hereinbefore defined.

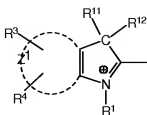
Claim 13. A compound according to claim 1 wherein said group $-E-F$ comprises a carboxypentyl group.

Claim 14. A compound according to claim 1 selected from:

- i) 2-((1*E*,3*E*,5*E*)-5-[1-(5-carboxypentyl)-3-methyl-5-sulpho-3-(4-sulphobutyl)-1,3-dihydro-2*H*-indol-2-ylidene]penta-1,3-dienyl)-1-ethyl-3-methyl-3-(4-sulphobutyl)-3*H*-indolium-5-sulphonate;
- ii) 2-((1*E*,3*E*,5*E*)-5-[1-(5-carboxypentyl)-3-methyl-5-sulpho-3-(4-sulphobutyl)-1,3-dihydro-2*H*-indol-2-ylidene]penta-1,3-dienyl)-3-methyl-1,3-bis(4-sulphobutyl)-3*H*-indolium-5-sulphonate;
- iii) 2-((1*E*,3*E*,5*E*,7*E*)-7-[1-(5-carboxypentyl)-3-methyl-5-sulpho-3-(4-sulphobutyl)-1,3-dihydro-2*H*-indol-2-ylidene]hepta-1,3,5-trienyl)-1-ethyl-3-methyl-3-(4-sulphobutyl)-3*H*-indolium-5-sulphonate;
- iv) 2-((1*E*,3*E*,5*E*,7*E*)-7-[5-(carboxymethyl)-3-methyl-1,3-bis(4-sulphobutyl)-1,3-dihydro-2*H*-indol-2-ylidene]hepta-1,3,5-trienyl)-1-ethyl-3-methyl-3-(4-sulphobutyl)-3*H*-indolium-5-sulphonate; and
- v) 1-benzyl-2-((1*E*,3*E*,5*E*)-5-[1-(5-carboxypentyl)-3-methyl-5-sulpho-3-(4-sulphobutyl)-1,3-dihydro-2*H*-indol-2-ylidene]penta-1,3-dienyl)-3-methyl-3-(4-sulphobutyl)-3*H*-indolium-5-sulphonate.

Claim 15 (withdrawn): A method for preparing a compound according to claim 1, the method comprising:

- a) reacting a first intermediate compound having the formula (A):



(A)

wherein Z^1 , R^1 , R^3 , R^4 , R^{11} and R^{12} are hereinbefore defined;

- b) a second intermediate compound which may be the same or different from the first intermediate compound and having the formula (B):



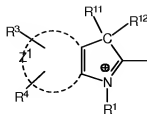
(B)

wherein Z^2 , R^2 , R^5 , R^6 , R^{13} and R^{14} are hereinbefore defined; and

- c) a third compound (C) suitable for forming a linkage between the first and second compounds;

provided that at least one of the groups R^1 , R^2 , R^3 , R^4 , R^5 and R^6 is the group $-E-F$, where E and F are hereinbefore defined; and provided that one or more of groups R^{11} , R^{12} , R^{13} and R^{14} are independently selected from the group $-(CH_2)_k-W$, where W is selected from sulphonic acid and phosphonic acid groups and k is an integer from 1 to 10.

Claim 16 (withdrawn): A compound of formula:



wherein:

groups R^3 and R^4 are attached to the Z^1 ring structure, wherein Z^1 is hereinbefore defined;

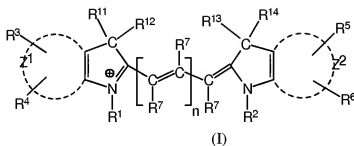
at least one of the groups R^1 , R^3 and R^4 is the group $-E-F$ where E and F are hereinbefore defined;

at least one of groups R^{11} and R^{12} is the group $-(CH_2)_k-W$, where W is selected from sulphonic acid and phosphonic acid groups and k is an integer from 1 to 10.

Claim 17 (withdrawn): A compound according to claim 16 wherein $-(CH_2)_k-W$ is selected from $-(CH_2)_3-SO_3H$ and $-(CH_2)_4-SO_3H$.

Claim 18 (withdrawn): A method for labeling a target component, the method comprising:

- i) contacting said component with a compound of formula (I):



wherein:

groups R^3 and R^4 are attached to the Z^1 ring structure and groups R^5 and R^6 are attached to the Z^2 ring structure, and $n = 1, 2$ or 3 ;

Z^1 and Z^2 independently represent the carbon atoms necessary to complete a one ring, or two-fused ring aromatic system;

at least one of groups R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 is the group $-E-F$ where E is a single

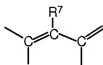
bond or a spacer group having a chain from 1–20 linked atoms selected from the group consisting of carbon, nitrogen and oxygen atoms and F is a target bonding group;
one or more of groups R^{11} , R^{12} , R^{13} and R^{14} are independently selected from the group –
 $(CH_2)_k-W$, where W is sulphonic acid or phosphonic acid and k is an integer from 1 to 10;

when any of groups R^1 and R^2 is not said group –E–F, said remaining groups R^1 and R^2 are independently selected from $C_1 - C_6$ alkyl, benzyl either unsubstituted or substituted with sulphonic acid, and the group $-(CH_2)_k-W$, where W and k are hereinbefore defined;

when any of groups R^3 , R^4 , R^5 and R^6 is not said group –E–F, said remaining groups R^3 , R^4 , R^5 and R^6 are independently selected from hydrogen and sulphonic acid;

when any of groups R^{11} , R^{12} , R^{13} and R^{14} is not said group $-(CH_2)_k-W$, said remaining groups R^{11} , R^{12} , R^{13} and R^{14} are independently $C_1 - C_6$ alkyl;

remaining groups R^7 are hydrogen or two of R^7 together with the group,



form a hydrocarbon ring system having 5 or 6 atoms; and

- ii) incubating said fluorescent dye with said component under conditions suitable for binding to and thereby labeling said component.

Claim 19 (withdrawn): A method according to claim 18 wherein said component is selected from the group consisting of antibody, lipid, protein, peptide, carbohydrate, nucleotides which contain or are derivatized to contain one or more of an amino, sulphhydryl, carbonyl, hydroxyl and

carboxyl and thiophosphate groups, and oxy or deoxy polynucleic acids which contain or are derivatized to contain one or more of an amino, sulphhydryl, carbonyl, hydroxyl, carboxyl and thiophosphate groups, microbial materials, drugs, hormones, cells, cell membranes and toxins.

IX. EVIDENCE APPENDIX

Appellants hereby present the following patent:

US Patent No. 6,974,873 (“Leung”).

This patent is relied upon by the Examiner for rejection of appealed Claims 1-6 and 10-14 in the final Advisory Action Before Filing an Appeal Brief dated July 22, 2009.

X. RELATED PROCEEDINGS APPENDIX

There are no other appeals or interferences related to the instant appeal.